region, wherein the enhanced promoter region is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the promoter region.

88. A method for constructing the vector of claim 84, comprising operatively linking together the nucleic acid molecule and the polypeptide coding sequence.

89. A method for producing the vector constructed in claim 88, comprising introducing the vector into a host cell that is capable of replicating the vector and allowing the host cell to replicate the vector.--

REMARKS

Introductory Comments:

Claims 26 and 60-80 were examined in the Office Action dated June 15, 1995 (Paper No. 8) and rejected based on: (1) 35 U.S.C. § 112, second paragraph, as indefinite (claims 60-80); (2) 35 U.S.C. § 112, first paragraph, as nonenabled (claims 60-80); (3) 35 U.S.C. § 102(b) as anticipated (claims 60-80); and (4) 35 U.S.C. § 103 as obvious (claims 62 and 73-75). These rejections are believed to be overcome in part by the amendments and are otherwise traversed for reasons discussed below.

Applicants note that although claim 26 was indicated as being rejected on page 1 of the present Office Action, no specific grounds of rejected were set forth therein. Accordingly, clarification is requested.

Overview of the Amendments:

Claim 73 has been cancelled without prejudice or disclaimer. It is to be understood that cancellation of the claim is not meant to be an acquiescence to any outstanding rejections, and applicants reserve the right to bring the claim again in a subsequent, related application.

Claims 60, 65-67, 71 and 76-79 have been amended. In particular, claim 60 has been amended to recite the relative arrangement of the elements in the polynucleotide sequence. Claim 60 has also been amended to recite that the transcription regulatory region is "capable of directing" the transcription of an operably linked polypeptide coding sequence. Support for these amendments can be found, *inter alia*, in Figure 29, and in the specification at, for example, page 24, lines 11-25; and page 57, lines 6-13.

Claim 65 has been amended to recite a vector having a transcription regulatory region that includes a polynucleotide sequence that is homologous to the first HCMV IE1 intron proximal to a 3′ end of the promoter of human cytomegalovirus immediate early region, HCMV IE1. Support for the amendment can be found, *inter alia*, in Figure 29, and in the specification at page 58, lines 3-7.

Claim 66 now recites that the SV40 polyadenylation region is derived from plasmid pSV7d. Support for the amendment can be found in the specification at page 57, lines 29-31. Claim 67 has been amended to correct an inadvertent typographical error, and now recites that the SV40 origin of replication is derived from plasmid pSVT2. Support for the amendment can be found in the specification at page 57, lines 31-34.

Claim 71 has been amended to particularly recite a polynucleotide sequence homologous to a sequence present in plasmid pCMV6ARV120tpa. Support for the amendment can be

found, *inter alia*, in the specification at page 57, lines 7-25.

Claim 76 now recites that the transcription regulatory region is "capable of directing" the transcription of an operably linked downstream polypeptide coding sequence. Support for the amendment can be found, *inter alia*, in the specification at page 24, lines 11-25; and at page 57, lines 6-13. Claim 77 has been amended to recite a vector that is arranged in the same manner as plasmid pCMV6a. Support for the amendment can be found, *inter alia*, in Figure 29, and in the specification at page 57, line 6 through page 58, line 7.

Claim 78 has merely been amended to more particularly recite the method. Claim 79 has been amended to specify that the intron's position is proximal to the 3' end of the promoter region derived from a transcription regulatory region of HCMV IE1. Support for the amendment can be found, *inter alia*, in Figure 29, and in the specification at page 57, line 35 through page 58, line 7.

New claims 81-89 have been added and are directed to further embodiments of the claimed invention. Support for the new claims can be found at page 48, lines 15-19; page 57, line 6 through page 58, line 7 and Figure 29.

Accordingly, no new matter has been added to the application by way of the above amendments and the new claims.

<u>The Petition for Correction of Inventorship Pursuant to 37 CFR §1.48(c)</u>:

The Examiner denied the Petition for Change of Inventorship under 37 C.F.R. § 1.48(c) (the "Petition") filed March 27, 1995 on the grounds that "inventor Hallewell has not signed the Declaration."

Applicants have now been able to obtain inventor Robert A. Hallewell's signature. Accordingly, reconsideration and acceptance of the Petition is earnestly solicited.

Entry of the Supplemental Amendment in SN 08/107,377:

Applicants acknowledge with appreciation the Office's acceptance of the Supplemental Amendment from SN 08/107,377, and the insertion of pages 145-148 into the instant specification as indicated in the present Office Action.

The Rejections under 35 U.S.C. §112, Second Paragraph:

The Office Action rejected claims 60-80 under 35 U.S.C. § 112, second paragraph, as being "indefinite for failing to particularly point out and distinctly claim the subject matter applicants regard as the invention."

More particularly, the Action asserts that claim 60 is "unclear because the arrangement of the elements in relation to each other is unspecified. It is also unclear how a transcription regulatory region can 'cause' transcription." (Paper No. 8, page 2).

Claim 60 has been amended to point out with greater particularity the relative arrangement of the elements. Furthermore, the transcription regulatory region is herein defined as being "capable of directing" the transcription of a polypeptide coding sequence. Accordingly, this basis for rejection is believed moot.

The Action also asserts that "it is unclear in claims 64, 66, 67, 75, 79 and 80 what it means to be derived from as there is no clear relationship linking the starting and ending material so as to warrant the conclusion that one was derived from the other." (Paper No. 8, page 2.) This rejection is now moot as the present claims do not contain this language.

The Office Action also rejected claim 65 under § 112, second paragraph, asserting that it "is unclear ... whether the intron is one which is 3′ to the HCMV IE1 promoter or if it is any intron which is positioned 3′ to the HCMV promoter." (Paper No. 8, page 2). The present claim 65 clearly points out that the claimed vector comprises a second polynucleotide sequence that is homologous to the first HCMV IE1 intron. Thus, applicants submit that the instant rejection is moot.

The Action also rejected claims 66, 67, and 77 under 35 U.S.C. § 112, second paragraph, on the grounds that "the limitation 'constructed in the same manner' is unclear since it could refer to the process steps involved or to the genetic elements employed in the vector." (Paper No. 8, page 2). However, this language is absent from the present claims 66 and 67. Further, claim 77 now recites a vector that is "arranged in the same manner as plasmid pCMV6a." Thus, applicants respectfully submit that the instant grounds of rejection are moot. Reconsideration and withdrawal thereof is earnestly solicited.

Claims 67, 71 and 79 were also rejected under 35 U.S.C. § 112, second paragraph, on the grounds that: "usage of 'a' in claim 67 is confusing" and that "it is unclear whether the intent of claim 71 is to the deposited plasmid" and that "'a' 3′ end" is improper. (Paper No. 8, page 2). However, the "a" that was objected to is no longer in claim 67, and claim 71 recites the plasmid pCMV6ARV120tpa. Claim 79 specifies that the intron's position is proximal to the 3′ end of HCMV IE1. Therefore, these grounds of rejection are moot.

Applicants note that the Office Action has provided no specific grounds of rejection of independent claims 76 and 78 under 35 U.S.C. § 112, second paragraph. Thus, the

rejection of those claims under § 112, second paragraph is believed improper, and applicants respectfully request withdrawal thereof. If the Office intends to maintain the rejection of the subject claims under 35 U.S.C. § 112, second paragraph, applicants request that the Office clarify its position by providing specific grounds of rejection of those claims in writing so that applicants may appropriately respond thereto.

The Objections and Rejections under 35 U.S.C. §112, First Paragraph:

The specification was objected to, and claims 60-79 rejected, under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide support for the invention as now claimed. More particularly, the Office asserts:

> There is no written description of the genus of expression vectors set forth in claims 60-79. The specification contains a single example of a fragment derived from HCMV which example does not set forth the individual elements of the claimed genus so as to permit construction of other members of the genus. (Paper No. 8, page 3).

Applicants disagree. Specifically, claim 79 is not drawn to an expression vector. Rather, the claim expressly recites an intron comprising a nucleotide sequence homologous to a sequence present in the first intron proximal to the 3′ end of HCMV IE1 promoter region. Thus, the instant grounds of rejection regarding the vectors of claims 60-78 does not properly apply to claim 79.

Moreover, this intron is described in the specification at, for example, page 58, lines 2-7. An example of the presently claimed vector is also described in the specification at, for example, Figure 29 and page 57, line 6 through page 58, line 7. Applicants submit that enablement

may be achieved through the use of illustrative examples. Non-enablement occurs only when "there is reason to doubt the objective truth" of the specification. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). Furthermore, there is no requirement under 35 U.S.C. § 112 for an inventor to make and test all of the species within the scope of a generic claim. *In re Angstadt*, 190 USPQ 214 (CCPA 1976).

Thus, in the present instance, the Office Action has failed to establish a *prima facie* case that a person skilled in the art would be unable to practice the presently claimed vectors or intron given applicants' teaching herein. Accordingly, the rejection herein is improper.

For all of the foregoing reasons, applicants submit that the objection to the specification, and the rejection of claims 60-79 under 35 U.S.C. § 112, first paragraph is in error. Reconsideration and withdrawal thereof is respectfully requested.

The Office Action further objected to the specification, and rejected claims 79-80 under 35 U.S.C. § 112, first paragraph as "failing to adequately teach how to make and/or use the invention." Particularly, the Office asserts:

> The specification does not provide guidance as to how to make the intron [of claims 79-80]. Nor does the specification teach how to use the intron. While the specification teaches the inclusion of the intron in a larger fragment containing the enhancer-promoter, there is no guidance as to how to make and use the intron. (Paper No. 8, pages 3 and 4, bridging paragraph).

Applicants disagree. Particularly, applicants note that their charge under 35 U.S.C. § 112, first paragraph is to provide a specification which teaches one of ordinary skill in the art how to make and use the claimed invention without "undue experimentation." *In re Wright*, 27 USPQ2d

1510 (Fed. Cir. 1993). Nothing more than objective enablement is required, and such enablement is judged by the standards of those skilled in the art.

Applicants have described how to "make" the intron of claims 79 and 80. Figure 29, and the specification at pages 57 and 58, describe in detail the various components and the construction of the CMV IE-1 expression vector pCMV6a. The intron of claims 79 and 80 can be readily obtained from the HCMV IE1 promoter region contained in the subject vector using recombinant techniques that are well known in the art.

Further, applicants have described how to "use" the intron of claims 79 and 80. In this regard, the inclusion of the subject intron in a mammalian expression vector is described at page 57 and the vector was shown to provide a significant increase (e.g., a 50-100 fold increase) in the expression of gp120 polypeptide relative to an SV40-based expression system.

Thus, applicants have provided an enabling disclosure which describes how to "make and use" the intron of claims 79 and 80. Reconsideration and withdrawal of the objection to the specification, and the rejection of claims 79 and 80 under 35 U.S.C. § 112, first paragraph is respectfully requested.

The Office Action also objected to the specification, and rejected claims 79-80 under 35 U.S.C. § 112, first paragraph on the grounds that the specification "does not provide support for the invention as now claimed." Specifically, the Action asserts that

> There is no written description of the intron as an individual entity. It is described as part of a larger construct and there is nothing in the specification to suggest that it was viewed as a separate and distinct invention as of the time of filing. (Paper No. 8, page 4).

Applicants disagree. Applicants note that the Office has not identified any legal grounds which would prevent them from presenting claims drawn to one particular aspect or combination of elements of their invention, wherein that aspect (or combination) has utility separate and apart from other aspects of the invention.

Further, applicants note that claims 79 and 80 of the application as originally filed clearly and distinctly claim the subject introns as part of the present invention. The Office is reminded that an original claim complies with the Section 112 invention description requirement. *In re Koller*, 204 USPQ 702, 706 (CCPA 1980). As indicated above, the presently claimed intron is described and the specification is enabling in teaching one skilled in the art how to make and use the intron. Thus, applicants have met the legal requirements of 35 U.S.C. § 112, first paragraph. Nothing more is required. The Office Action has failed to establish a *prima facie* case of lack of enablement. Accordingly, this rejection is improper. Reconsideration and withdrawal of the objection to the specification, and the rejection of claims 79 and 80 under 35 U.S.C. § 112, first paragraph is earnestly solicited.

The Rejections under 35 U.S.C. §102(b):

The Office Action has rejected claims 60, 61 and 63-72 under 35 U.S.C. § 102(b) as being "clearly anticipated" by Foecking et al. The Action asserts that

> Foecking et al (1986) discloses an expression vector which contains an SV40 origin of replication, an SV40 polyadenylation site, the HCMV E1 promoter-enhancer, an SV40 splicing site, a bacterial origin of replication, an ampicillin resistance gene as a selectable marker and the chloramphenicol acetyltransferase gene as a

reporter for assessment of promoter-enhancer activity. (Paper No. 8, page 5).

Applicants respectfully disagree. In particular, "anticipation" of a claim under §102 *requires* each and every element as set forth in the claim to be disclosed in a *single* prior art reference. *See, e.g., Davis v. Loesch*, 27 USPQ2d 1440 (Fed. Cir. 1993); *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913 (Fed. Cir. 1989). Foecking et al. fails to "anticipate" claims 60, 61 and 63-72, as the reference fails to set forth each and every element of the subject claims.

Specifically, Foecking et al. describe a construct that contains a 619 bp fragment derived from HCMV strain AD169 which includes the major immediate early gene enhancer and associated promoter sequences. This 619 bp fragment corresponds to nucleotide positions -522 to +97 relative to the cap site (see Figure 1, page 103 of Foecking et al.).

In contrast, applicants' vectors contain a 1.7 kbp *Ssp*I-*Sal*I fragment derived from HCMV Towne strain, which includes the region encoding the first exon (5' untranslated), the first intron and the start of the second exon (see, applicants' specification, page 57, line 35 through page 58, line 6). Thus, applicants' construct includes an HCMV fragment that is nearly three times the size of the fragment present in the construct described by Foecking et al.

Further, the Office Action has mischaracterized the vector described by Foecking et al. The pCMV*cat* construct described by Foecking et al. does <u>not</u> include an SV40 origin of replication, and it is established law that the exclusion of a single claimed element from a reference is enough to negate anticipation by that reference. *Atlas Powder Co. v E.I. du Pont De Nemours & Co.* 224 PQ 409, 411 (Fed Cir.

1984); *Kalman v. Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983). In this regard, Figure 1, (page 103) of Foecking et al. depicts the construction of pCMV*cat*. The subject vector contains three segments: (1) a 2.1-kb *Acc*I fragment containing the Ap-resistance gene derived from pBR322; (2) the major immediate early gene enhancer and promoter sequences from HCMV strain AD169 derived from pCM5029; and (3) a 2.3-kb fragment derived from pRSV*cat*, including the CAT coding region and the early SV40 splice and polyadenylation signal.

Claim 60, in contrast, expressly recites a vector comprising a polynucleotide sequence having an SV40 origin of replication. Claims 61 and 63-72 all depend from claim 60, and thus include all the limitations of that claim including an SV40 origin of replication. Since Foecking et al. fails to describe a construct that includes an SV40 origin of replication, the reference fails to anticipate claims 60, 61 and 63-72.

For all of the foregoing reasons, reconsideration and withdrawal of the rejection of claims 60, 61 and 63-72 under 35 U.S.C. § 102(b) is respectfully requested.

The Office Action also rejected claims 60-80 under 35 U.S.C. § 102(b) as "clearly anticipated" by Chapman et al. Applicants respectfully submit that this rejection is also improper.

More particularly, the Office has acknowledged that a "written description of an expression vector containing the human cytomegalovirus immediate early region (HCMV E1) occurs in SN 07/138,894 with a filing date of December 24, 1987." (Paper No. 8, page 4). Applicants note that the present application derives from that application (Serial No. 07/138,894). Further, applicants have claimed, and are

entitled to the priority of, the December 24, 1987 filing date of Serial No. 07/138,894 pursuant to 35 U.S.C. §120. Chapman et al., however, published in 1991. Accordingly, the reference is not prior art and therefore not properly citable against the present claims under 35 U.S.C. § 102(b). Reconsideration and withdrawal of the rejection of claims 60-80 under 35 U.S.C. § 102(b) is thus respectfully requested.

The Rejections under 35 U.S.C. § 103:

The Office Action rejected claim 62 under 35 U.S.C. § 103 as being "unpatentable over Foecking et al." More particularly, the Action asserts that

> It is well known in the art to insert a plurality of restriction enzyme sites into linker regions so as to permit the correct orientation of the inserted sequence. It would have been obvious ... to employ a linker containing a *Sal*I site in order to facilitate the correct insertion of a sequence of interest which itself contained one or more *Sal*I sites. (Paper No. 8, page 6).

Applicants disagree, and respectfully submit that the Office has failed to make a *prima facie* showing of obviousness over Foecking et al. Particularly, in order for the Patent Office to establish its required *prima facie* case of obviousness (and shift the burden of going forward to applicants), it must establish that Foecking et al. would have suggested each and every limitation of the claimed invention to those of ordinary skill in the art. In this regard, the Court of Appeals for the Federal Circuit states:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art ... Both the suggestion and the expectation of success must be found in the

> prior art, not in the applicant's disclosure. *In re Dow Chemical*, 5 USPQ2d 1529, 1531-1532 (Fed. Cir. 1988).

Any departure from the prior art must be evaluated in terms of the whole invention, including whether the prior art provides any teaching or suggestion to one of ordinary skill in the art to make the changes that would produce applicants' claimed invention. *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ2d 1321 (Fed. Cir. 1990).

As discussed above, Foecking et al. fail to describe a construct which includes applicants' recited 1.7 kbp HCMV fragment and an SV40 origin of replication. Further, Foecking et al. fail to suggest that expression vectors, such as those recited in claim 63, should be constructed to include the SV40 origin of replication. The Office's reliance on an asserted "art recognition to employ a linker containing a *Sal*I site in order to facilitate the correct insertion of a sequence of interest" in an expression vector fails to establish a teaching, suggestion or motivation which can be combined with Foecking et al. to produce applicants' claimed invention. Thus, the Office has failed to establish a *prima facie* showing of obviousness showing of obviousness over Foecking et al. Reconsideration and withdrawal of the rejection of claim 63 under 35 U.S.C. § 103 is thus respectfully requested.

The Office Action also rejected claim 73 as allegedly being "unpatentable over the combined teachings of Foecking et al. in view of the arts recognition of the importance of gp120 of HIV as represented by Luciw et al. (US Patent 5,156,949)." (Paper No. 8, page 6). The Action further asserts that "Luciw et al. is available as prior art under the provisions of 35 U.S.C. § 102(e). Luciw et al. is relied upon for its teachings of the coding sequence of HIV

gp120 and the arts interest in gp120 for the analysis of viral infection." (*Id.*)

Claim 73 has been cancelled. Thus, the rejection thereof is moot.

The Office Action also rejected claims 74 and 75 under 35 U.S.C. § 103, asserting that the claims are "unpatentable over the combined teachings of Foecking et al. and van Zonneveld et al." More particularly, the Action asserts:

> van Zonneveld et al. discloses expression vectors for the expression of human tissue-type plasminogen activator and in particular demonstrates that the signal sequence is effective even with truncated coding sequences. (Paper No. 8, page 7).

The Office Action also takes particular note of the disclosure of the present invention discussing van Zonneveld et al., and argues:

> It would have been obvious to a person of ordinary skill in the art ... to include a signal sequence to facilitate the secretion or membrane association of a polypeptide of interest, particularly wherein only a portion of the polypeptide of interest is being expressed, and more specifically to utilize the signal sequence element taught by van Zonneveld et al. (Paper No. 8, page 7).

Applicants disagree, and respectfully submit that the instant rejection is improper. Particularly, it is again noted that Foecking et al. fails to describe or suggest applicants' vectors that contain the recited 1.7 kbp HCMV fragment or the SV40 origin of replication. The van Zonneveld et al. reference fails to provide the missing motivation or suggestion to arrive at applicants' invention. The Office's attempt to use the teaching provided by applicants' disclosure to piece together van Zonneveld et al. and Foecking et al. to arrive at the subject matter of claims 74 and 75 is merely a hindsight reconstruction of

applicants invention--using applicants' own disclosure as prior art.

It is well established that the Office cannot use a claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *In re Fritch* 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("one cannot use hindsight reconstruction to pick and chose among isolated disclosures in the prior art to deprecate the claimed invention.")

The Office Action has failed to identify the requisite teaching or motivation from the prior art which would lead to applicants' invention. Without the benefit of applicants' disclosure, there is no motivation or suggestion to one of ordinary skill in the art to combine Foecking et al. with van Zonneveld et al. to produce the vectors of claims 74 and 75. Thus, it is submitted that the instant grounds of rejection is improper. Reconsideration and withdrawal of the rejection of claims 74 and 75 under 35 U.S.C. § 103 is respectfully requested.

The Additional Art Made of Record:

Applicants have considered the additional prior art made of record (and not relied upon) by the present Office Action (Paper No. 8, pages 8-10), and acknowledge the Office's position that the subject art does not affect the patentability of the present invention.

Conclusion

Applicants respectfully submit that the claims define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art.

Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

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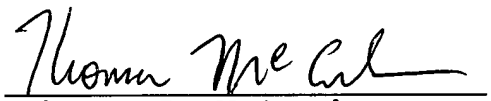
By: 

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